An initiative of NSW Clinical Pharmacologists & Pharmacists
Funded by the NSW Department of Health

LOW MOLECULAR WEIGHT HEPARINS,

HEPARINOIDS & HIRUDINS

A Position Statement of the NSW Therapeutic Assessment Group Inc.

1994
Updated February 1997
Revised August 1999

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EXECUTIVE SUMMARY

Low molecular weight heparins *(LMWHs)* are fragments of standard **unfractionated heparin (UH)** formed by depolymerisation by different methods of manufacture. The **heparinoid, danaparoid,** is a mixture of heparan, dermatan and chondroitin. It is through the predominant inactivation of Xa that heparinoids and LMWHs produce their indirect anti-thrombotic action. **Desirudin,** a recombinant form of hirudin, is a direct thrombin inhibitor, is indicated in the prevention and treatment of thromboembolic disorders and may be used in the treatment of heparin-induced thrombocytopenia (HITs).

The advantages of LMWHs over UH include:

1. A higher degree of bioavailability by the subcutaneous route;
2. Longer elimination half-life compared with UH, allowing once or twice a day dosing, and outpatient treatment;
3. Predictable pharmacokinetics and pharmacodynamics not requiring routine monitoring except in patients with renal dysfunction or extremes of weight or body shape;
4. Low to moderate inhibition of platelet function.

Recommended indications

Surgery: In patients undergoing major *orthopaedic surgery* LMWHs, heparinoids and hirudins are equivalent or superior to UH and Dextran 70 in reducing the risk of deep vein thrombosis (DVT). For thromboprophylaxis in *low risk medical* and *surgical* patients, analysis of trials to date suggests that LMWHs have no clinically important benefit over UH. However, in high risk medical patients LMWHs may be more effective than UH, with possibly decreased risk of bleeding. Optimal duration of treatment post-operatively depends on the type of operation and patient risk factors.

DVT: Studies suggest that LMWHs are as effective and safe as standard therapy for DVT, while offering the advantage of subcutaneous administration without the need for monitoring in most cases. Use of these agents on an outpatient basis reduces treatment costs. LMWHs are at least as effective as UH in the treatment of pulmonary emboli *(PE)*, although larger studies need to be carried out for this therapy to become routine.

Cardiology: LMWHs are indicated in *unstable angina and non-q-wave myocardial infarction. Dalteparin* has been shown to be equivalent to UH. Enoxaparin and nadroparin may be superior to UH in reducing the incidence of death or recurrence in this group of patients. Further trials are underway to confirm these results. Prolongation of treatment with LMWH after the acute phase is still controversial.

Other indications in which LMWHs have been shown to be effective are in anticoagulation regimens for patients undergoing *haemodialysis,* thromboprophylaxis in *oncology* patients, during *pregnancy* and in *children.* Indications still under investigation include use in neurosurgery, spinal cord injuries and stroke.

Danaparoid has low cross-sensitivity with heparin and is a more suitable alternative to both heparin and LMWH in patients with *HITs*.

Side effects

Increased bleeding is the major side effect of all these agents. Dosages may need to be reduced in elderly patients and patients with decreased renal function. Care should be taken in patients undergoing procedures such as epidural cannulation and anaesthesia.

Conclusions

Direct comparison between various LMWHs in adequate clinical trials has not been made. Therefore at present they are not interchangeable. In some cases, intravenous UH is a better choice. It may be more cost-effective for inpatients, more suitable in patients with a high risk of bleeding and in peri-operative use, as its shorter half-life means therapy can be discontinued more quickly than LMWH. Although acquisition costs of LMWHs are greater than for UH, savings are possible in other areas such as decreased thromboembolic disease recurrence and complications, shortening of hospital stay, increased outpatient treatment of DVT, decreased monitoring costs and improved quality of life for patients.

1. INTRODUCTION

Heparin was described by Maclean as a medical student in 1916 and has been the mainstay of prevention and treatment of thromboembolism.[1] The development of low molecular weight heparins (LMWH) occurred in the mid 1970s with the observation that fractions prepared from standard unfractionated heparin (UH) lose their ability to prolong activated partial thromboplastin time (APTT) while maintaining their ability to inhibit factor Xa.[2] The impetus for development was further enhanced by the observations that low molecular weight heparins produce less bleeding in animal models than UH.[2] Dalteparin (*Fragmin*, Pharmacia & Upjohn) was the first LMWH to be launched on the Australian market in May 1991 followed by enoxaparin (*Clexane*, Rhone-Poulenc Rorer) and nadroparin (*Fraxiparine, Fraxiparin Forte*, Sanofi-Winthrop).

LMWHs available overseas include: tinzaparin, certoparin, parnaparin, reviparin and ardeparin.
Danaparoid (*Orgaran*, Organon) is a low molecular weight heparinoid. Desirudin (*Revasc*, Rhone-Poulenc Rorer), a recombinant hirudin, is the most recent addition to this group of anticoagulants.

1.1 Pharmacology and Pharmacokinetics

The blood coagulation process involves two pathways, the extrinsic and intrinsic. A common pathway shared by both starts with the conversion of factor X to Xa. This then activates prothrombin (II) to thrombin (IIa). Thrombin then potentiates the conversion of soluble fibrinogen to fibrin, which is involved in clot formation.

Unfractionated heparin (UH) is extracted from either porcine gastrointestinal mucosa or beef lung.[1,3] Heparin from these sources is a heterogenous mixture of pentasaccharide chains with a molecular weight of 2,000-40,000D (mean of 15,000D). Heparin acts predominantly through the binding of its pentasaccharide sequence to antithrombin III (ATIII)[3], which is a plasma glycoprotein that acts as a serine protease inhibitor. The native circulating ATIII form has a low affinity for serine proteases. When bound to the pentasaccharide sequences of heparin its activity is markedly increased[3].Thus activated, its inhibition of the clotting factors X, II plus VII, XI and IX is potentiated. Heparin inactivates thrombin by acting as a template for both ATIII and thrombin. This complex formation requires longer chain lengths (>18 monosaccharide units). Heparin also acts through heparin cofactor II which requires even longer monosaccharide chain lengths (>24 monosaccharide units).[2]

The inactivation of Xa does not require complex formation and thus can be achieved with shorter chain lengths (<18 monosaccharide units). **Low molecular weight heparins (LMWHs)** are fragments of UH that have a mean molecular weight between 4,000D to 6,500D.[2,3,4] They are manufactured by a variety of methods, producing differing distributions of chain lengths.[2] The ATIII activity against IIa relies on longer (>18 monosaccharide unit) chains for activity. Consequently, LMWH retains full anti-Xa with relatively less anti-IIa (thrombin) activity. Different LMWHs with similar mean molecular weights can have different effects on thrombin, depending on the nature of the chains produced.[5,6]

TABLE 1. Differences between the heparins and related substances.[5,6,7,8,9,10,12,14]

[illegible] (METHOD OF PREPARATION) [illegible]	[illegible] UNIT [illegible]	ANTI-FACTOR [illegible] RATIO	[illegible]	[illegible] WEIGHT (DALTONS)	HALF-LIFE [illegible]	BIO-AVAIL-ABILITY [illegible]	ELIMINATION	[illegible] CLEARANCE [illegible]
Dalteparin Nitrous acid depolymerisation	10,000	2.0:1	142	5,000	iv: 2 hours sc: 3-4 hours	80-90%	Renal	33
Enoxaparin Benzylation/ Alkaline Depolymerisation	10,000 = 100mg	2.7:1	54	4,500	sc: 4.4hours	Over 90%	Liver metabolism, renal excretion	16
Nadroparin Fractionation/ Nitrous acid Depolymerisation	9,500	3.2:1	95	4,500	sc: 3.5hours	98%	Renal	21
Danaparoid	1,250	20:1	-	6,500	sc/iv: Anti-Xa Activity : 25hrs. Thrombin generation inhibition: 7 hrs	Approx. 100%	Renal	-
Desirudin		-	-	7,000	sc: 0.6-2 hours	Approx. 100%	Metabolised and eliminated by the kidney	80
Unfractionated Heparin		1:1	170	15,000 (Range: 3,000 - 30,000)	Dose and time-dependent iv: 30 -120min sc: 1- 4 hours	10-30%	Saturable: Binds to reticulo-endothelial system, liver, spleen. Nonsaturable renal excretion.	39 (Depends on assay).

Despite the clinical effectiveness of LMWHs, their mechanism of action is not completely understood. For example, they may cause release of endogenous factors such as tissue factor pathway inhibitor and prostacyclins at different amounts, depending on the type of LMWH. A direct comparison of these agents in biological units (anti-Xa) is not available.[7]

As the LMWHs vary both biochemically and pharmacologically (see Table 1), each one may have its own activity for each indication. As the clinical significance of these variations is unknown, it is not recommended to extrapolate results from one low molecular weight heparin to another[3,8,9,10], although this has been done in various meta-analyses (see section 2).

Danaparoid (previously ORG 10172) is prepared from porcine gut mucosa after the removal of heparin.[2,11] It is a mixture of heparan sulphate (85%), dermatan sulphate (10%) and chondroitin sulphate (5%).[12] The anticoagulant effect of danaparoid is characterised by the high ratio of anti-factor Xa/antithrombin activity, resulting in an effective inhibition of thrombin generation and formation with minimal bleeding activity. Danaparoid has a negligible effect on platelet function and has a longer half-life than LMWH.[12]

Desirudin (previously CGP 39393) is a recombinant polypeptide resembling hirudin, the substance produced in the peripharangeal glands of the medicinal leech (*Hirudo medicinalis*), but differing from hirudin by the absence of a sulphate group on tyrosine.[13] Desirudin prolongs the clotting time, whether induced directly (thrombin time), or indirectly via the intrinsic (aPTT) or extrinsic (PT) pathways. Unlike heparin, which is a protease inhibitor and a weak inhibitor of clot-bound thrombin, hirudins are direct thrombin inhibitors, which inhibit clot-bound as well as fluid-phase thrombin.[14]

Other ATIII-independent thrombin and factor Xa inhibitors are available experimentally: hirudin fragments, argatroban, hirugen, tick anticoagulant peptide (TAP) and leech anti-coagulant peptide (antistasin).[15]

2. CLINICAL TRIALS

2.1 Thromboprophylaxis in surgery

The risk of thromboembolic complications in patients undergoing major surgery is well reported.[16] Age and surgery-related factors affect the risk of development of deep venous thrombosis (DVT).[17] Low risk patients for DVT are those younger than 40 undergoing uncomplicated surgery or those over 40 undergoing minor surgery.[18] Patients aged over 40, obese patients and those undergoing general surgery are at moderate risk.[18] The *high risk group* includes patients undergoing major orthopaedic surgery, patients with a recent history of thrombophlebitis and those over the age of 40 undergoing extensive pelvic and abdominal surgery for malignancy.[18] In the high risk general surgical group calf vein thrombosis occurs in 40-80% and proximal vein thrombosis in 10-20%.[21] Pulmonary emboli (PE) occur in 1-5% of this high-risk group.[18] Approximately 50% patients undergoing total hip replacement will develop deep vein thrombosis (DVT) and 4-7% will develop pulmonary emboli.[16-18] Thromboprophylaxis with heparin has been shown to reduce the risk of venous thromboembolism.[16,19,20] Optimal duration of therapy post-operatively depends on

type of operation and patient risk factors. Age, history of thromboembolic disease, malignancy, obesity and immobilisation should be considered when continuing prophylaxis beyond hospital discharge.

Koch et al[21] performed a meta-analysis of 36 individual, randomised, controlled studies in patients undergoing general (including gynaecological, urological and malignant diseases) or orthopaedic surgery, where one group was treated with LMWH and compared with another group treated with UH, dextran or placebo. Clinical endpoints were venous thrombosis of the lower limbs and/or PE, major bleed or death. In general surgery, there was no increased efficacy in favour of high dose LMWH (Odds Ratio = 0.88; 95%CI: 0.80,1.05; p=0.53), but there was a higher risk of bleeding complications (OR 1.47; 95%CI: 1.07,2.01: p=0.02). Low dose LMWH was equally efficacious (OR 1.03 ; 95%CI: 0.85,1.26), but safer than UH (OR 0.68; 95%CI: 0.56,0.82; p<0.01). In orthopaedic surgery, there was a trend towards an increased efficacy for LMWH (OR 0.83; 95%CI: 0.68,1.02) with equivalent safety (OR 0.96; 95%CI: 0.68,1.36). The analysis of studies had clearly outlined objectives, review criteria and methods of pooling and assessment of heterogeneity. However, criteria for assessing validity and methods of applying validity criteria were not discussed. Also, because of the heterogeneity of studies (e.g. types of patients, variations in diagnostic methods, different LMWH used), the generalisability of the results is limited. However, previous meta-analysis as well as individual trials support these conclusions.[22]

2.1.1 General Surgery

Several trials have compared dalteparin with both placebo and conventional UH in the prevention of post-operative thrombosis in general surgery. Most trials involved patients age 40 years and over undergoing elective general abdominal surgery with the outcome of thromboembolism defined as detection of DVT using I^{125} fibrinogen uptake tests.

Kakkar[23] compared dalteparin 2,500 units subcutaneously (sc) daily with UH 5,000 units sc twice a day in 3,900 patients over 40 years of age, undergoing abdominal surgery. There was a non-significant reduction in major bleeding in the LMWH group (3.6% LMWH vs 4.8% UH; p=0.10) and an increased incidence of wound haematoma (1.4% LMWH vs 2.7% UH; p=0.007) in those receiving UH. No significant differences were found in the efficacy of the two agents.

Enoxaparin has been compared in a dose of 60, 40 and 20mg daily with UH given in a dose of 5,000 units sc three times a day.[24] All three LMWH regimens were equivalent to UH in their ability to reduce thromboembolism. Bleeding complications were reported to be higher in patients receiving 60mg enoxaparin compared with UH. The incidence was similar for the 40mg and 20mg doses. It should be noted that the dose of UH used is greater than that generally accepted for prophylaxis of general surgery of moderate risk. Two meta-analyses[22,25] and a study by Nurmohamed[26] have suggested no clinically important benefit of LMWH over UH in general surgical patients.

2.1.2 Orthopaedic Surgery

Several trials have compared enoxaparin, dalteparin and danaparoid with standard UH therapy and placebo in the prevention of thromboembolism after orthopaedic surgery.

In patients undergoing total hip replacement, dalteparin in a dose of 5,000 units daily was shown to be superior to placebo in reducing the incidence of venous thrombosis as detected by the I^{125} reuptake test.[27] The authors noted that the development of DVT was also delayed in the treatment group with more patients in the placebo group developing DVT in the first 4 postoperative days. This delay may be important since it could allow the patient to become more mobile and therefore further reduce the risk of DVT. Compared with UH given in a dose of 5,000 units sc three times a day, dalteparin in a dose of 5,000 units daily was equivalent in its ability to reduce DVT.[28] It was noted that the thromboembolism that did occur in the dalteparin group tended to be distal rather than proximal. There was a significantly lower incidence of pulmonary embolism in patients receiving dalteparin compared with UH (p=0.016). Patients receiving dalteparin had significantly fewer bleeding complications compared with UH treatment.

In orthopaedic patients undergoing hip replacement enoxaparin in a dose of 30mg sc twice a day is superior to placebo in reducing the incidence of deep vein thrombosis.[29] Of those who developed DVT, patients receiving enoxaparin had a significantly greater incidence of distal rather than proximal DVT. Similarly, in knee surgery enoxaparin at a dose of 30mg twice a day was shown to reduce the incidence of deep vein thrombosis.[30] When compared with standard prophylactic regimens enoxaparin has been as effective in reducing the incidence of thrombosis.[31-33] When compared with 7,500 units of UH given subcutaneously twice a day, a twice daily dose of 30mg of enoxaparin resulted in similar incidences of total and proximal DVT.[31] When compared with Dextran 70, enoxaparin was shown to be superior in reducing the incidence of deep vein thrombosis.[32] Similarly, enoxaparin 40mg once a day was shown to be superior to UH given 5,000 units 3 times a day in patients undergoing elective hip replacement.[33] The incidence of bleeding complications on enoxaparin therapy is similar or less than that reported for the alternative treatment.[31]

The length of treatment needed post-operatively and the timing of the first prophylactic dose are factors which vary between American and European centres. For example, American centres generally do not give a preoperative dose, due to a perceived increased risk of bleeding. This factor may reduce the apparent efficacy of the LMWH and influence comparisons of LMWHs between studies.

Danaparoid has been shown in a randomised study to reduce the incidence of DVT to 12% at doses of 750 anti-Xa units twice a day, compared with dextran 70 (DVT incidence 31%) in patients undergoing surgery for hip fracture.[34] A study comparing danaparoid with aspirin also showed a significant reduction in the incidence of DVT in hip surgery.[35] The overall event rate, however, was much higher in this study than other studies with the incidence of total DVTs in the danaparoid group being 44.3% and 14% for proximal DVT. Further work is required to establish the relative efficacy of danaparoid with LMWH.

Desirudin has also been investigated for the prevention of DVT after hip replacement. A multi-centre, double-blind, randomised trial[36] compared 10mg, 15mg and 20mg desirudin given twice a day with 5000 iu three times a day of UH in patients undergoing total hip replacement. The results suggested a statistically significant reduction in thromboembolic events with all desirudin doses. The incidence of total thromboembolic events was 23.3%, 18.8% and 18.3% for 10mg, 15mg and 20mg

twice a day of desirudin compared with 33.6% for UH on an intention-to-treat basis. On a per-protocol basis, the relative risk reduction ranged from 30.1% to 48.2% for 10mg and 20mg twice a day of desirudin respectively. In two randomised placebo-controlled trials 998 patients undergoing elective hip surgery were randomised to either desirudin 15mg sc twice a day or UH 5,000 international units (iu) sc three times a day for 9–12 days. The rate of thromboembolic events in the desirudin groups was 13.5% vs 29.3% in the UH groups, representing an absolute risk reduction of 15.8%.[14] Desirudin 15mg sc twice a day was compared with enoxaparin 40mg sc daily in 1541 patients undergoing hip replacement surgery. 25.7% patients had a thromboembolic event in the enoxaparin group compared with 18.8% in the desirudin group ($p<0.01$).[14] However, further work is required to find out the relative efficacy compared with LMWHs, which are considered the most appropriate thromboprophylactic agents for this indication.[37]

2.2 Treatment of Deep Vein Thrombosis (DVT)

The main aims in treating patients with venous thromboembolism are to prevent both fatal and non-fatal PE, prevent recurrent thrombosis as well as extension of existing thrombosis while avoiding excess bleeding.[38] Standard therapy has been initial in-hospital treatment with intravenous (iv) heparin infusion adjusted for aPTT, followed by 3 months warfarin therapy with INR monitoring.[39] The advantage of sc treatment with LMWH is that monitoring is not required, leading to the possibility of outpatient treatment of DVT.

While individual studies to date have generally failed to find a difference in treatment effect between sc LMWH and iv UH, meta-analyses of early trials suggested LMWH may have advantages over UH.[40-43] These meta-analyses indicate that LMWHs have a statistically significant relative risk reduction of 50-60% for recurrence of thromboembolic events, major haemorrhage and overall mortality compared with iv UH. Later findings have not found a reduction of this magnitude, leading the Columbus group to conclude that LMWHs are associated with more modest reduction of 4-5%.[44] The rate of reduction in relative risk of recurrent thrombosis with UH may be due to the different regimens used in the studies.

A more recent meta-analysis was carried out by Leizorovicz[45], which showed that LMWHs were associated with statistically significant reduction in mortality, major haemorrhage and thrombus extension. A nonsignificant trend was seen favouring LMWH for thromboembolic recurrence. "LMWHs seem to have a higher benefit/risk ratio the UH in the treatment of venous thrombosis".[45] However, the analysis was based on trials with a short-term follow-up combining the results of different LMWHs and a single large trial has yet to be reported. Similarly, Van den Belt et al[39] reviewed 13 randomised clinical trials involving 4354 patients comparing adjusted dose iv or sc UH with fixed dosed once or twice a day LMWH (nadroparin, dalteparin, enoxaparin, reviparin , tinzaparin, CY222) in the treatment of venous thromboembolism. Twenty-five per cent of the patients included in the analysis had PE. They concluded that "compared with the current standard therapy with UH...the LMWHs demonstrated a statistically non-significant reduction in recurrent venous thromboembolism of approximately 25% during initial treatment, at 3 or 6 months follow up, or at the end of follow up". At the end of follow up 4.2% (n=76/1803 LMWH) vs 5.6% (n=101/1816 UH) patients had thrombotic complications. There was a significant

difference in venographic outcome favouring the LMWH group, as well as a significantly lower frequency of major haemorrhagic episodes (1.1% vs 2.0% UH). At the end of follow up 5.2% of 1803 LMWH patients had died compared with 6.9% in the UH group which was statistically significant. In the same paper, five studies with 1636 patients using nadroparin, tinzaparin and enoxaparin were analysed in patients with proximal DVT. There was a statistically significant reduction in the incidence of recurrent venous thromboembolic events in favour of LMWH (4.8% vs 7.8% UH) as well as a significant reduction in mortality (5.4% vs 8.3% UH).

It must be noted that meta-analysis may be flawed, due to changes in UH therapy regimens over time and the variability in results using different LMWHs.[46,47]

Non-monitored sc LMWH has the potential for home treatment of DVT. Hirsh[48] reported that 72% (73/102) of patients presenting to his thrombosis unit with acute DVT were successfully treated at home. Levine[49] conducted a study comparing sc enoxaparin administered primarily at home with an iv infusion of UH administered in the hospital. Patients were randomly assigned to receive either 1mg/kg of enoxaparin sc twice a day or adjusted dose iv UH for a minimum of 5 days. The incidence of thromboembolic events was similar in both groups with 5.3% and 6.7% of patients on enoxaparin and UH respectively having a recurrence of thromboembolic events ($p=0.57$). There were no differences in the rate of major or minor bleeding in each group and patients receiving enoxaparin were discharged earlier with an average length of stay of 1.1±2.9 days compared with 6.5±3.4 days for UH. In the study by Koopman et al,[38] 75% of patients randomised to nadroparin were discharged within 48 hours. The average bed stay was 2.7 days in the nadroparin group compared with 8.1 days for iv UH. Similar results have been found in an Australian study, comparing daily sc dalteparin at home with iv UH therapy.[50] These studies concluded that LMWH therapy for DVT was safe and effective and improved patients' quality of life.

Hirsh reviewed two studies comparing long-term enoxaparin and dalteparin with warfarin therapy.[41] Bleeding events occurred in 17 of 149 warfarin treated patients and 4 of 143 LMWH patients (Relative Risk Reduction 4.08), whereas 11 recurrences occurred in the LMWH group compared with only 6 in the warfarin group, a non-significant trend (RRR 0.52, $p=0.17$). Even if trials with larger numbers of patients showed a significant increase in LMWH efficacy compared with warfarin, LMWH is unlikely to replace warfarin, because of the convenience of oral therapy, increased cost of LMWH and long-term risk of osteoporosis with LMWH. However there may be a place for LMWH in patients intolerant of warfarin or unable to attend the laboratory for INR testing.

Danaparoid has also been investigated in the treatment of DVT.[11] 1250 anti-Xa units or 2000 anti-Xa units of danaparoid given twice a day were compared with iv UH adjusted by aPTT. The first dose of danaparoid was given iv with subsequent doses given sc. Oral anticoagulation was started on day two and parenteral treatment continued for a minimum of five days or until the oral anticoagulation dose had stabilised. Assessment of outcomes was done blinded to treatment regimens. The results suggest that 2000 units twice a day of danaparoid was significantly superior to UH in reducing the rate of recurrence or extension of thromboembolic events (11% vs 29% $p<0.05$). Danaparoid 1250 twice a day was not significantly different from UH.

Bleeding complications were not significantly different between the three groups. The limitations of this study are the small size (approximately 70 per arm) and the open design that may have influenced the outcome.

2.3 Treatment of Pulmonary Emboli

DVT and pulmonary embolism (PE) were previously treated as separate entities, but there is evidence now that they should be treated as one disease - venous thromboembolism (VTE).[44] The rate of PE, with or without DVT, is thought to be around 23 per 100,000 patients and is associated with 200,000 deaths in the US per year.[51] Primary treatment of PE is continuous infusion of UH in conjunction with oral warfarin for at least 3 months (USA) or 6 months (Australia). Current trials have shown VTE can recur after treatment (5-7%), but the death rate is under 5%.[38,44,52]

The THESEE (Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire)[52] study group randomised 612 patients with symptomatic PE to either *sc tinzaparin* (175 iu/kg sc daily) or UH (50 iu/kg iv bolus, then 500 iu/kg iv daily). All patients received oral anticoagulants, starting 1-3 days after heparin therapy was begun. The combined endpoint of death, symptomatic recurrent thromboembolism or major bleeding was measured at day 8 and day 90. Major bleeding rates were 2.6% for the UH group and 2% in the LMWH group. There was no significant difference in endpoints between groups during the three-month study period, leading to the conclusion that tinzaparin is a convenient alternative to UH in the treatment of symptomatic PE. In common with most trials in PE, the authors state that low patient numbers reduced the statistical power of the study and that 10,000 patients would be required for the study to show a statistically significant difference between the two treatments. They concluded that LMWH could be used in patients with acute PE, after those with haemodynamic instability were excluded.

The Columbus investigators[44] evaluated 1021 patients with either acute symptomatic DVT, PE or both. Patients were randomised to either fixed dose *reviparin sc bd* (4200iu, 6300iu or 3500iu, depending on body weight) or adjusted dose iv UH. Oral anticoagulation was started on day 1 or 2 and continued for 12 weeks. After 12 weeks there was no significant difference between the groups in terms of recurrent venous thromboembolic events (5.3% vs 4.9%UH group), major bleeding episodes (3.1% vs 2.3%) or mortality (7.1 vs 7.6%). However, the mean hospital stay was reduced by 3 days in the reviparin group, as 100 patients with DVT were treated as outpatients.

Smaller studies have been conducted with dalteparin, nadroparin and enoxaparin. Charland and Klinter reviewed five randomised clinical trials (433 patients) with PE, which compared LMWH and UH.[51] They concluded that although the data suggests that LMWH may be a safe and effective alternative to UH, more comparative clinical trials need to be carried out before LMWH therapy becomes a standard treatment for pulmonary embolism.

2.4 Anticoagulation for Haemodialysis

Haemodialysis requires the use of anticoagulants to maintain extracorporeal circuits by preventing fibrin deposition and thrombus formation. Heparin has been the mainstay of anticoagulation in haemodialysis for many years.[53] In haemodialysis patients, LMWHs have at least a similar efficacy and safety as UH, as has been shown in an analysis of 38 studies by Nurmohamed[5], but probably have no advantage over

UH in most patients.

2.5 Cardiac Indications

2.5.1 Unstable Angina/non-Q wave myocardial infarction (UA/NQMI)

The rupture of atheromatous plaque and subsequent formation of mural thrombus play a central role in the pathophysiology of acute coronary syndromes.[54] Heparin and aspirin each reduce the incidence and severity of ischaemic events after UA/NQMI and this combination is now the standard treatment to reduce the occurrence of ischaemia, MI and death.[55]

Dalteparin was evaluated in two large controlled trials. The **FRISC** (Fragmin during Instability in Coronary Artery Disease) study compared dalteparin (120 units/kg twice a day for 6 days, then 7500 units daily for 35-45 days) plus aspirin with aspirin alone.[56] At day 6 the incidence of composite endpoint (death/MI) was significantly lower for the dalteparin group (4.8% vs 1.8%). After 40 days with continued treatment of daily dalteparin 7500 units vs placebo, there was a trend in reduction in death and MI, which was no longer apparent at 4 to 5 months of follow up. The incidence of major bleeding complications were similar in both groups, however, minor bleeding complications were greater in the LMWH group (7.9% vs 0.3%).

As the FRISC trial did not use UH in the comparator group[57], the **FRIC** (Fragmin in Unstable Coronary Artery Disease) compared dalteparin (120iu/kg sc twice a day) and UH (5000iu iv then 1000iu/h, adjusted to aPTT, then sc UH twice a day)[58]. All patients (n=1482) received aspirin. After 6 days of therapy, the endpoint was similar for the two groups (7.6% in the UH group and 9.3% for dalteparin), with no added effect of dalteparin vs placebo after 45 days of continuous therapy. The incidence of major bleeding complications was similar for both groups (0.5% vs 0.4%) and there was a non-significant higher rate of minor bleeding events for the dalteparin group (5.1% vs 2.8% UH).

In the **ESSENCE** trial (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events)[59] patients were assigned to either *enoxaparin* (1mg/kg twice a day sc) or continuous iv heparin up to 8 days. After 14 days the composite end point was significantly lower among patients treated with enoxaparin (16.5% vs 19.8%for UH). This benefit was still apparent after 30 days, suggesting that a rebound increase in ischaemic events did not occur after cessation of enoxaparin, as is the case with UH. The incidence of major bleeding by day 30 did not differ between the two groups (6.5% vs 7.0%). The incidence of minor bleeding was higher in the enoxaparin group (13.8% vs 8.8% UH), primarily due to injection site ecchymoses.

The **TIMI IIB** (Thrombolysis in Myocardial Infarction) compares the efficacy of enoxaparin with that of standard heparin in the acute phase of MI/UA and with aspirin during the chronic phase to confirm the results of the ESSENCE study.[60] Patients (n=3910) received either heparin iv or enoxaparin 1mg/kg twice a day in hospital, followed by aspirin alone or enoxaparin 60mg or 40mg (weight-adjusted) sc every 12 hours for up to 43 days after discharge.

The variable clinical responses to different LMWHs in these trials may be due to both

the differences in the level of anti-Xa activity reached by different LMWHs and to their inate variance in inhibiting the various pathways in the clotting cascade.[55] Other variables between trials are both clinical (eg severity of disease in the patient population) and to do with trial design and endpoint definition.

The duration of therapy likely to best influence patient outcome has not yet been defined and is being investigated in TIMI IIb (enoxaparin) and FRISC II (dalteparin) trials.

Nadroparin, enoxaparin and dalteparin have also been investigated in smaller studies.[61,62] *Enoxaparin* is also being investigated in angioplasty in the ENTICES and ATLAST trials, and its use as adjunct therapy to tissue plasminogen activator for ST-elevation MI will come from HART-II.[60]

In current practice, UF is generally preferred to LMWH in invasive cardiac procedures because of its more rapid reversibility.

2.5.2 Hirudins

The hirudins have been investigated as adjuncts to thrombolytics in the treatment of acute myocardial infarction, in acute coronary syndromes and in percutaneous transluminal coronary angioplasties (PTCA).[63-68] In GUSTO-II (Global Use of Strategies to Open Occluded Arteries)[67] and TIMI-9 (Thrombolysis and Thrombin Inhibition in Myocardial Infarction) patients were randomised within 12 hours of onset of ischaemic pain to receive either standard heparin iv or hirudin (0.6mg/kg iv bolus followed by 0.2mg/kg/h). Both trials were suspended because of high incidence of bleeding in both groups.[66] Both heparin (1000 units/hr without weight adjustment) and hirudin (0.1mg/kg iv followed by 0.1mg/kg/h infusion for 3 to 5 days) were restarted at lower doses in TIMI 9B. A trend towards improved outcome (death and MI after 30 days) was observed with hirudin in GUSTO IIB, but not in TIMI-9b. The hirudin group had a high rate of bleeding complications (8.8% vs 7.7% in the heparin group p=0.03) in GUSTO, but the rate was the same in TIMI.

The HELVETICA trial investigated hirudin vs UH in the prevention of restenosis after PTCA.[63] The study compared a continuous infusion of UH with two dosing regimens of hirudin, either a bolus of 40mg followed by 0.2mg/kg/hour continuous infusion or a 40mg iv bolus followed by 40mg sc twice a day. The results suggested a reduction in events for hirudin compared with UH at 96 hours (11%, 7.9%, 5.6% for UH, iv hirudin and iv/sc hirudin respectively). However, there was no difference between the three groups for clinical events (32.7%, 36.5%, 32.0% respectively) or proportion of patients free of events at 7 months.

Concerns have been raised regarding the safety of the hirudins in combination with thrombolytics with several studies stopped early due to an excess of major haemorrhage.[67-69]

2.6 Other indications

2.6.1 Anticoagulation in patients with heparin-induced thrombocytopenia syndrome (HITS)

Heparin-induced thrombocytopenia syndrome is a well-recognised adverse effect of heparin therapy.[70] Two forms of HITS, type I and type II have been described. [71] Type I is the most frequent form, in which patients remain asymptomatic. The platelet count usually drops within 2 days of heparin exposure, but rarely falls below below $100x10^9$/L and may return to normal despite continued heparin therapy. Type II HITS is less frequent and is more severe, with platelet counts almost invariably falling below $100x10^9$/L and often below $40x10^9$/L. It develops 5-14 days after heparin exposure and may be complicated by arterial or venous thromboembolism in a small significant proportion of patients.[71,72] Mortality is estimated at 30% in patients with thrombotic complications.[71] The mechanism of type I HITS may be related to the platelet proaggregatory effects of heparin.[71] Type II HITS is mediated through an immune mechanism, triggered by antibodies directed against complexes of heparin and platelet factor 4 forming on the surface of platelets which activate Fc receptors.[7] LMWHs have been postulated to produce a lower incidence of HITS as they cause less activation of platelets and less release of platelet factor 4.[7] There are case reports of patients being successfully treated with enoxaparin.[73] However, as cross-reactivity is between 79 and 94%[74,75] it is recommended that LMWHs be avoided in these patients.[7]

Danaparoid sodium cross-reacts with heparin around 10% *in vitro*.[76] It has been used to treat 667 patients with HITS on a compassionate use basis.[76,77] A positive response (ie an increased platelet count without further thrombotic or bleeding complications) was achieved in 93% patients. Severe bleeding, persistant or recurrent thrombocytopaenia and development of new thromboembolic events occurred in 1.7-3.1% patients. Platelet aggregation in intensive care patients is greater than in the normal hospital population. Danaparoid has been shown to have the least propensity to cause platelet activation, compared with heparin and LMWH, which may be of advantage in this group of high-risk patients.[78] *Hirudin* can also be used to treat HITS.[7,76]

Tests for cross-reactivity to LMWH and danaparoid may guide management.

2.6.2 Pregnancy

Studies suggest that, like heparin, *heparinoids and LMWHs* do not cross the placenta[79] and are rated pregnancy risk category C* by ADEC[80], due to "increased incidence of human loss and prematurity associated with haemorrhage". However this rating is controversial, as heparin, if effectively monitored, has been used for prophylaxis and treatment during pregnancy for several years worldwide.[81] The use of LMWHs in pregnancy has been investigated in both small open studies and case reports, without maternal or foetal complications.[82-85] Both enoxaparin and dalteparin have been used as prophylactic agents in pregnant women. The general opinion is that LMWH can be considered as an alternative to standard heparin in pregnant women requiring anti-thrombotic prophylaxis[81], however major trials are lacking. Appropriate care should be taken in patients receiving epidural anaesthesia during labour (see section 3.1.1). *Desirudin* is Category B3*. It has been shown to be teratogenic in animal studies and

there is inadequate clinical experience to support its use in pregnant women.[14]

* Category C: Drugs are those which owing to their pharmacological effect have caused or may be suspected of causing harmful effects on the human foetus or neonate without causing malformations [56].
* Category B3: Drugs which have been taken by a limited number of pregnant women without increasing the frequency of malformation or other direct or indirect harmful effects on the human foetus. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which in humans is unknown.

2.6.3 Paediatrics

Heparin therapy in children is especially problematic because of delays in achieving therapeutic and constant aPTT plus the trauma of repeated venepunctures required for monitoring. Guidelines for adults cannot be extrapolated to children because of anticipated differences in clearance and interaction with the developmentally immature system of the young.[86] *Enoxaparin* 1.6 units/kg (newborns) or 1mg/kg (up to 17 years) sc every 12 hours was used to treat 25 children with DVT, PE, thrombotic complications or heart disease in a dose-finding Canadian study.[87] There were no new thrombotic events during treatment (mean 14 days). Direct comparisons with UH have not been made and experiences using other LMWH have not been published.

2.6.4 Malignancy

Cancer patients are more prone to have a hypercoaguable state due to many factors such as direct activation of the clotting system by neoplastic cells, synthesis of procoagulants by mononuclear cells, injury of endothelial cells by cancer cells and chemotherapeutic agents and defective platelet function.[88] Prandoni et al[89] reported a randomised trial of symptomatic patients with proximal vein thrombosis. Patients were given either fixed dose (adjusted to weight) sc twice a day fraxiparin or adjusted dose iv UH for 10 days, followed by 3 months of oral warfarin. Recurrent venous thromboembolism did not differ between groups, but showed a significant reduction with LMWH in deaths from cancer; 8/18 (44%) cancer patients died in the UH vs 1/15 (7%) in the LMWH group; p=0.021, at the end of six months' follow up. Combining this data with the mortality data from a similar trial by Hull[90], reveals 21 deaths in 67 cancer patients in the UH arms (31%) compared with 7 in 47 with LMWH (15%), p=0.005.[91] It is speculated that therapy with LMWH may have an antitumor effect, possibly by inhibition of tumor angiogenesis.[92]

TABLE 2. Tabular Analysis of Significant Clinical Studies Mentioned In The Text

Citation (Ref.)	Study type	Study Population	Intervention	Outcomes	Results	Conclusions	Costs / Benefits
Koch 1997 (21)	MA	16,583 patients for general or orthopaedic surgery 36 studies	LMWH vs UH	Rate of DVT/PE, Bleeding complications, Death	General surgery efficacy of low dose LMWH: OR 1.03 (0.85-1.26 P=0.76) Orthopaedic: OR 0.83 (0.68-1.02 P=0.07)	Heterogeneity affects the analysis and generalisation of results to other patients.	LMWH may be equally efficacious in general surgery with less bleeding. LMWH may be more efficacious than UH in orthopaedic surgery with equivalent safety.
Kakkar 1993 (23)	Multi-centre PRDB	3809 patients undergoing major abdom surgery. Pts controlled for age (>40), sex, NSAIDs, malignancy	Dalteparin 2,500 units sc daily vs UH 5,000 units sc twice daily x 5 days	DVT/PE, Postoperative bleeds, death 4 week follow-up	No sig. Diff. in blood loss, less wound haematoma in LMWH group, fewer patients required further surgery. No sig. diff. in end-points	Dalteparin and UH of similar efficacy. Prolonged prophylaxis not justified in this setting	Major bleeds: 69/1894 vs 91/1915 (p=0.058). 23 % reduction in bleed (NS) DVT/PE; 0.9% vs 0.6%(UH) Deaths after follow-up: 10/1661 vs 9/1698 (UH).
Eriksson 1991 (28)	PRDB	136 patients (>40yo) elective total hip replacement	Dalteparin 5,000 units sc daily vs UH 5,000 units sc three times daily x 10 days	DVT/PE Blood loss	PE:8/65 vs19/62 UH (p=0.016) Thrombosis: 19/63 vs 25/59 UH (NS)	Overall incidence of DVT similar. LMWH prevented proximal thrombosis and PE and decreased transfusion needs.	Bleeding complications: post-op. blood loss and amount of blood transfused during and after operation significantly higher in the UH group.

Levine 1991 (31)	PRDB	665 patients (>40y.o.) hip replacements in 5 hospitals	Enoxaparin 30mg sc twice daily vs calcium heparin 7,500units sc twice daily x 14days	Venous thrombosis, haemorrhage	Thrombosis: 50/258 vs 61/263 UH (p>0.2). Proximal DVT: 14 vs 17 UH (p>0.2)	NS in incidence of DVT, no symptomatic PE. Reduction in bleeding for LMWH.	Bleeding: 17/333 vs 31/332 UH (p=0.035) RRR 45% Major bleed: 11 (3.3%) vs 19(5.7%) UH (p=0.103). Transfusion needs: NS
Citation	**Study type**	**Study population**	**Intervention**	**Outcomes**	**Results**	**Conclusions**	**Costs / Benefits**
Borris 1991 (32)	PR	219 patients (>18 y.o.) elective total hip	Enoxaparin 40.6mg sc daily vs Dextran 70	DVT, blood loss	DVT: 7/108 vs 24/111dextran (p=0.0013) No clinical PE	Enoxaparin has greater efficacy with similar safety	Bleeding: NS during operation . Post-op blood loss and transfusions: Higher in dextran group (p=0.0044, p=0.025)
Bergqvist 1991 (34)	PR Three hospital	289 patients hip fracture.	Danaparoid 750units sc vs dextran 70 x 10 days	DVT, bleeding 8 week follow-up	DVT: 12% vs 31% dextran (p<0.001)	Danaparoid sig. better thromboprophylactic effect than dextran. Transfusion difference probably due to the haemodilution effect of dextran.	Mortality after 2 months NS (6.2% vs 5.5% dextran) 3 fatal PE in dextran group vs 0 in danaparoid group. Post-op transfusions greater in dextran group (p<0.01)
Eriksson 1996 (36)	DBPR Multi-centre Europe	1119 elective hip surgery	Hirudin 10, 15, 20mg sc twice daily vs UH 5000units sc three times daily x 8-11 days	DVT/PE Death	DVT: 23.9%, 18.4%, 17.7% vs 34.2% UH (P=0.0113, 0.0003, 0.0001). RRR by hirudin: 30-48% for DVT and 57-88% for proximal DVT.	Hirudin is significantly more effective than UH in prevention of thromboembolic disease after hip surgery	No difference in peri-operative or post-operative blood loss. Total blood loss increased in 20mg hirudin group. No difference in bleeding complications.

Prandoni 1992 (89)	PR Multi-centre Europe	170 veno-graphically proven proximal DVT (PE excluded)	Nadroparin sc twice daily weight-adjusted vs iv UH	Symptomatic DVT/PE Follow–up 1,3,6 months	Recurrence: 7% vs 14% UH. (p=0.13)	Efficacy and safety similar in LMWH and UH group. Recurrences and bleeding incidence similar to previous reports. Future studies should examine the imbalance in cancer deaths.	UH group: 3 fatal PE, 2 thrombocytopenia. LMWH: 3 fatal PE. Severe bleeding: 1% vs 4% UH (p>0.2). At 6 mths mortality7% vs 14% UH (p=0.21). 67% deaths in UH group due to malignancies. 44% of cancer pts died in UH group, but only 7% in LMWH group.(p=0.021)
Citation (Ref.)	**Study type**	**Study population**	**Intervention**	**Outcomes**	**Results**	**Conclusions**	**Costs / Benefits**
Van den Belt 1998 (39)	MA	PE(25%pts.) / DVT initial treatment. 13 studies/ 4352 patients	LMWH (six brands) vs iv or sc UH	Recurrence of symptomatic DVT/PE Mortality	Recurrent disease at the end of follow-up: 63/1702 (3.7%)LMWH vs 86/1713 (5%)UH after 3mths: OR 0.77	Adopt LMWH as standard therapy with DVT. Await further results for pts. with PE. Statistical test for heterogeneity neg.	Major haemorrhage: 23/2158 (1.1%) vs 43/2196 UH (2%) (OR 0.55). Result in favour of LMWH. Mortality: overall 5.2% vs 6.9% in UH group. (OR=0.74) In malignant disease: result in favour of LMWH
Levine 1996 (49)	PR Multi-centre, Canada	500 patients Symptomatic proximal DVT	Enoxaparin 1mg/kg vs iv UH	Recurrent thrombosis 3 month follow-up Bleeding	VTE (3mths): 13/247 (5.3%) vs 17/253(6.7%) UH. RRR=22% p=0.57	Using LMWH to treat DVT/PE at home increases convenience and decreases costs.	Major bleeding:5/247 vs 3/253 UH p=0.5 2 fatal PE in UH group 2 fatal bleeds in LMWH group 11 deaths in LMWH vs 17 in UH group Mean hospital stay: 1.1 days vs 6.5 days in UH.

Koopman 1996 (38)	PR Multi-Centre Inter-national	400 patients with acute symptomatic proximal DVT	Nadroparin adjusted for weight vs iv UH	24 week follow-up Recurrent thrombosis Bleeding QOL, use of resources	Recurrence:14/202 (6.9%) vs 17/198 (8.6%)UH One fatal PE in UH group, 2 fatal PE in LMWH group	Reduction of 67% in the duration of hospitalisation in LMWH group. 75% were discharged early or never admitted.	Major bleeds: 0.5% vs 2%UH Minor bleeds; 13% vs 7%UH Mortality: 6.9% vs 8.1%UH QOL: overall no sig. diff. between groups. Mean hospital stay: 2.7days vs 8.1days UH
THESEE 1997 (52)	PR multi-centre France	612 patients with symptomatic PE	Tinzaparin sc daily vs iv UH Follow-up 90 days	Recurrent PE/DVT Bleeding Deaths 90 day follow-up	18/304 (7.1%) vs 22/308 (5.9%) UH reached at least one endpt. Documented recurrence: 5/304 vs 6/308 UH (NS)	The rates of recurrence, bleeding, death in both groups were similar and low.	Major bleed: 2% vs 2.9% UH at day 90. 3 in each group died of PE
Citation (Ref.)	**Study type**	**Study population**	**Intervention**	**Outcomes**	**Results**	**Conclusions**	**Costs / Benefits**
Columbus 1997 (44)	PR Multi-centre Inter-national	1021pt. Acute symptomatic DVT and/or PE	Reviparin sc twice daily weight adjusted vs iv UH	Recurrent DVT/PE Major bleeding Mortality 12 week follow-up	Recurrent DVT/PE: 5.3% vs 4.9% UH (NS)	Fixed dose LMWH is as effective and safe as UH regardless whether the patient has PE or a history of venous thromboembolism.	Both for length of hospital stay, length of therapy-NS. However 100 patients with DVT were treated as outpatients. Major bleed: 3.1vs2.3%(NS) Mortality: 7.1vs7.6% (NS) Three pts in each group had fatal PE.
FRISC 1996 (56)	DBPR Placebo control Multi-centre Sweden	1506 UA/NQWMI	Dalteparin 120iu/kg sc twice daily x 6 days, then 7500iu/d x 35-45days vs placebo. Both groups: aspirin 75mg/day	Death/AMI 150 day follow-up	Day 6: 1.8% vs 4.8% placebo (p=0.001) Day 40: 8% vs 10.7% placebo (p=0.07) Day 150: 14% vs 15.5% placebo (p=0.41).	Dalteparin and aspirin recommended for at least 6 days in this pt. group. Long-term treatment needs further assessment. Criticism of trial: used placebo control.	Incidence of major bleeds similar to placebo (0.8% vs 0.5%), but minor bleeds increased (8.2% vs 0.3% placebo).

FRIC 1997 (58)	Open acute phase (d 0-6) DB (d6-45) Multi-centre Inter-national	1482 UA/NQWMI	Dalteparin 120iu/kg/12h vs UH iv then sc x 5-8 d. Both groups: aspirin 75-165mg/day	Death/AMI/ Recurrent angina Revascularisation Major bleeding Follow-up at 6 day and 45 days.	Days 0-6 Death/MI/angina: 9.3% vs 7.6%UH (RR 1.18, p=0.33). Death or MI: 3.9% vs 3.6% (p=0.8) Day 45 death/AMI/angina: 12.3% each group.	Dalteparin sc bd is an alternative to UH in the acute phase of treatment.	Major bleeding day 6: 1.1% vs 1% (NS). Day 45: 0.5% vs 0.4% NS. Revascularisation: NS (14.3% each group)
Citation (Ref.)	**Study type**	**Study population**	**Intervention**	**Outcomes**	**Results**	**Conclusions**	**Costs / Benefits**
ESSENCE 1997 (59)	DB PR Multi-centre Inter-national	3171 UA/NQWMI	Enoxaparin sc 1mg/kg/12h vs iv UH up to 8 days. Both groups: aspirin 100-325mg daily.	Death, AMI, recurrent angina, major & minor haemorrhage, coronary revascularisation. 30 day follow-up	At 14 days risk of angina, MI, death : 16.6% vs 19.8% UH (p=0.019) At 30 days;19.8% vs 23.3% UH (p=0.001)	Enoxaparin plus aspirin is more effective than UH plus aspirin. Increase in incidence of minor bleeding only in the LMWH group.	30 day incidence major bleed: 6.5% vs 7% UH (NS). Overall bleeds: 18.4% vs 14.2% UH (p=0.001).

AMI	=	acute myocardial infarction
DB	=	double blind
MA	=	metaanalysis
NQWMI	=	non-Q wave myocardial infarction
NS	=	not statistically significant
OR	=	odds ratio
PR	=	prospectively randomised
QOL	=	quality of life
RRR	=	relative risk reduction
UA	=	unstable angina

2.6.5 Indications under review[5]

- Spinal cord injury
- Trauma and intensive care patients
- Post myocardial infarction
- Moderate risk surgery e.g. colorectal, abdominal, in obese patients.
- Oncology patients undergoing surgery
- Desirudin for HITS

2.6.6 Equivocal results

- Ischaemic stroke[93]
- Cardiopulmonary bypass surgery[5]
- Neurosurgery[5]

2.6.7 Routine usage not supported by the evidence

- Routine prophylaxis of low risk general surgery[21]
- General medical patients[21]
- PTCA, coronary stenting and other arterial thrombus disease states[62].

3. ADVERSE EFFECTS AND INTERACTIONS

3.1 Bleeding Frequency

Haemorrhagic complications with LMWHs compared with UH may theoretically be less because of their reduced propensity to cause thrombocytopenia, their lower affinity for von Willebrand factor, weaker effect on platelet function and lower tendency to increase vascular permeability.[94] However, from the balance of evidence in clinical trials, there is no significant difference in the incidence of major bleeding when LMWHs are compared with UH.[95]

Risk factors for bleeding complications with patients undergoing LMWH therapy include: high doses of LMWH, patients who have undergone surgery in the previous 10 days, patients taking antiplatelet, anticoagulant, thrombolytic agents or medications which may increase the risk of haemorrhage, patients with a history of bleeding diathesis and trauma.[96] Measured anti-Xa levels have failed to predict bleeding risk.

Clinically, the most common complication associated with LMWH is haematoma at the injection site.

3.1.1 Regional anaesthesia during LMWH prophylaxis

In December 1997, the FDA alerted health professionals to the increased risk of epidural or spinal haematomas when LMWHs or heparinoids are given concurrently with spinal or epidural anaesthesia or when its administration is temporally related to spinal puncture.[97]

A review article by Horlocker and Heit[98] gave guidelines for management of regional anaesthesia in patients receiving perioperative heparins and concluded that regional anaesthesia in association with perioperative heparins is safe and effective with appropriate patient selection and anaesthetic technique.The authors suggested that needle placement should occur at least 10-12 hours after the last LMWH dose. Subsequent dosing should be delayed for at least 2 hours after needle placement. Catheter removal should be delayed for at least 10-12 hours after a dose of LMWH and preferrably for 24 hours. Again, subseqent dosing should not occur for 2 hours after catheter removal

Boxed warnings are now required in product information approved by the FDA for LMWH and heparinoids.[99] Similar warnings are listed under "precautions" in Australian LMWH product information.[8,9,10,12] Specific guidelines for use of enoxaparin in epidural anaesthesia/analgesia have been provided by the manufacturer.[8]

In his study using *hirudin* in patients undergoing total hip replacement surgery, to avoid haematomas, Eriksson gave the first dose after regional-block anaesthesia but just before the start of surgery.[28] The combination of hirudins with thrombolytics has been associated with an unacceptably high rate of serious bleeding complications. This may, however, be due to the high doses used in early trials[67-69] and may be resolved by careful monitoring to ensure aPTT does not exceed 100sec[13] or 85 sec.[14]

3.2 Thrombocytopenia

A drop in platelet count within 1-2 days of starting therapy is due to the proaggregatory effect of heparin on platelets and is rarely serious.[71] Immune-mediated thrombocytopenia usually develops after 5-10 days' treatment and may be associated with severe venous and/or arterial thromboses. The incidence of HITS with UH is 2-3% but is less with LMWH.[5] In a study published in 1995[100] a total of 665 patients were randomly assigned to receive either LMWH or UH. Thrombocytopenia was defined as a platelet count less than 150,000/mm.[3] There were 9 patients (2.7%) in the UH group who developed thrombocytopenia. Eight of the 9 patients suffered one or more thrombotic events, compared with none in the LMWH group.

3.3 Osteoporosis

Osteoporosis is a well-documented side effect of long-term UH therapy. Two to three percent of patients receiving UH for more than 3months develop symptomatic bone fractures.[101] The potential of LMWHs to produce osteoporosis is uncertain. Animal data suggests that LMWHs in equipotent doses produce the same degree of osteoporosis.[102] Preliminary human data so far suggests that LMWHs may have less effect on bone density.[103] In a randomized study of 80 patients with venous thromboembolism, who had contraindications to oral anticoagulants, dalteparin (5,000u sc twice daily) was shown to reduce the rate of vertebral fractures compared with UH therapy (10,000IU sc twice daily).[104] At 6 months, the incidence of osteoporosis was lower in patients given twice daily sc LMWH than in those given UH (2.6% vs 17.6% p=0.054). This study, however, was too small to detect any

meaningful differences in the rate of hip fracture, an outcome with more serious morbidity and mortality than vertebral fracture.

3.4 Other Adverse Effects

Transient moderate elevations of liver transaminases have been observed. Allergic reactions such as urticaria, anaphylaxis, hypertension, fever, pruritus and bullous eruptions at the injection site have been rarely observed.[8,9,10,12]

3.5 Overdose: Reversal by Protamine

Protamine reverses the effects of LMWH incompletely. Studies have suggested that protamine can reverse the bleeding effect despite only moderate reductions in the anti-Xa activity.[105-107] One mg of protamine neutralises the anti-IIa activity, but only partially neutralises the anti-factor Xa activity generated by 1mg (100 iu anti-Xa activity) of enoxaparin or 100units dalteparin.[94] Six mg protamine neutralises about 0.1mL (950 iu) nadroparin.[10]

Reduced effectiveness of protamine sulphate is not only a feature with LMWHs, but also with heparinoids and it is completely ineffective against desirudin. However, the rapid clearance of hirudins may mean a reversal agent may not be required.[13]

3.6 Contraindications [8-10,12,14]

Since LMWHs are derived from heparin, they have the same contraindications as heparin. Listed contraindications are: sensitivity to heparin, documented HITs, haemorrhagic diathesis, haemorrhagic stroke, active peptic ulcer, severe hypertension, endocarditis.
Patients with haemostatic defects may be best treated with UH, due to its shorter half-life.

3.7 Monitoring

LMWHs and heparinoids do not usually affect the aPTT. LMWH therapy is monitored using a specific anti-Xa assay.[94] A target plasma range of 0.5-1.0 iu anti-Xa activity/mL is usually advised with peak levels measured 4 hours after s.c. injection.[94] It has been generally considered that monitoring is not required[7] at doses of less than 5000 units anti-Xa per day (5000 units dalteparin or 40mg enoxaparin) and in uncomplicated cases. Fixed dose regimens both in the prophylaxis of DVT and the treatment of DVT have been efficacious without the need to adjust doses based on monitoring.[89,90] It is recommended that platelet counts be monitored two or three times a week, while the patient is on LMWH treatment (Concord Hospital protocol, NSW, February 1999).

Monitoring should be carried out in patients with renal failure and in some elderly patients (see below). In patients weighing over 100kg, the initial dose of enoxaparin should be limited to 100mg twice daily and anti-Xa levels should be monitored 3 to 5 hours after the morning dose on day 2 and every second day thereafter and the dose modified if necessary (Concord Hospital protocol, February 1999). Paediatric patients receiving LMWH should have anti-Xa levels routinely monitored.[86,87]

Hirudins: APTT should be monitored in patients with increased risk of bleeding complications, hepatic and/or renal impairment and patients receiving thrombolytics

or anticoagulants. The aPTT should not exceed 85 or twice the upper limit of normal aPTT and should be measured 4 hours after the start of infusion, then once daily.[14]

4. RECOMMENDED INDICATIONS

Surgery: In patients undergoing major *orthopaedic surgery* LMWHs, heparinoids and hirudins are equivalent or superior to UH and Dextran 70 in reducing the risk of deep vein thrombosis (DVT). For thromboprophylaxis in *low risk medical* and *surgical* patients, analysis of trials to date suggests that LMWHs have no clinically important benefit over UH. However, in high risk medical patients LMWHs may be more effective than UH, with decreased risk of bleeding. Optimal duration of treatment post-operatively depends on the type of operation and patient risk factors.

DVT: Studies suggest that LMWHs are as effective and safe as standard therapy for DVT, while offering the advantage of subcutaneous administration without the need for monitoring in most cases. Use of these agents on an outpatient basis reduces treatment costs. LMWHs are at least as effective as UH in the treatment of pulmonary emboli *(PE)*, although larger studies need to be carried out for this therapy to become routine.

Cardiology: LMWHs are indicated in *unstable angina and non-q-wave myocardial infarction. Dalteparin* has been shown to be equivalent to UH and enoxaparin and nadroparin may be superior to UH in reducing the incidence of death or recurrence in this group of patients. Further trials are underway to confirm these results. Prolongation of treatment with LMWH after the acute phase is still controversial.

Other indications in which LMWHs have been shown to be effective are in anticoagulation regimens for patients undergoing *haemodialysis,* thromboprophylaxis in *oncology* patients, during *pregnancy* and in *children.* Indications still under investigation include use in neurosurgery, spinal cord injuries and stroke.

Danaparoid has low cross-sensitivity with heparin and is a more suitable alternative to both heparin and LMWH in patients with *HITS.*

4.1 Recommended doses [8,10,12,14]

4.1.1 Prophylaxis against thromboembolism

Dalteparin: 2,500 units given 1-2 hours before the operation and 2,500 units sc every morning until the patient is mobilised.
**High risk general surgery:* 5,000 units given the evening before the operation and then 5,000 units subcutaneously each evening until the patient is mobilised.
Orthopaedic surgery: 5,000 units the evening before operation and 5,000 units the following evenings, continued for five weeks.

Enoxaparin: **High risk medical/surgical patients:* 40mg given 12 hours before

surgery and then continued at a dose of 40mg once a day until the patient is mobilised. *Moderate risk:* 20mg sc daily, starting 2 hours before an operation, for 7 to 10 days.

Nadroparin: *General surgery*: 0.3mL (2,850iu) daily sc for at least 7 days or until patient is ambulant. The first dose to be given 2-4 hours pre-operatively.
The initial dose for *orthopaedic surgery* should be given 12 hours before surgery and 12 hours after the end of surgery. Treatment should then be once a day for at least 10 days.

Weight	Pre-op. and until day 3	From day 4 onwards
40-60kg	0.2ml daily	0.3ml daily
61-80kg	0.3ml daily	0.4ml daily
81-124kg	0.4ml daily	0.6ml daily

Danaparoid: 750 anti-Xa units twice daily for 7 –10 days.

Desirudin: 15mg sc twice daily, starting within 30 minutes of surgery and continuing for 9 to 12 days. If regional anaesthesia is to be used, give the first dose after induction of anaesthesia.

* High risk" of thromboembolism: Age over 40 years, history of DVT or PE, surgery or other trauma, prolonged immobilisation, cardiac disease, obesity, malignancy, varicose veins, hypercoaguable states, pregnancy and the puerperium, oral contraceptives, severe infection, inflammatory bowel disease.[108]

4.1.2 Treatment of Deep Vein Thrombosis

Dalteparin: 100 units/kg twice a day by subcutaneous injection or 100 units/kg continuous iv over 12 hours.

Enoxaparin: 1.5mg/kg given once a day or 1mg/kg given sc twice a day (in high-risk patients*) for 5 to 10 days. Monitoring at this dose is not required.

Nadroparin: twice a day sc for at least 10 days.

Weight	Doses given twice a day
<50kg	0.4ml
50-59kg	0.5ml
60-69kg	0.6ml
70-79kg	0.7ml
80-89kg	0.8ml
90kg	0.9ml

4.1.3 Anticoagulation for Haemodialysis

Dalteparin: For patients at low risk of bleeding undergoing haemodialysis for more

than 4 hours the recommended dose is a bolus of 30-40 units/kg followed by an iv infusion of 10-15 units/kg/hr. For patients undergoing haemodialysis of < 4 hours, a single iv bolus dose of 5,000 units can be used. Plasma levels should be maintained at 0.5-1 anti-Xa units/ml. In patients undergoing dialysis who have a high risk of bleeding a lower dose of 5-10 units/kg dalteparin followed by an iv infusion of 4-5 units/kg/hr is used. Plasma levels should be kept between 0.2-0.4 anti-Xa units/ml.

Enoxaparin: In patients undergoing haemodialysis of < 4 hours duration and with low bleeding risk the recommended dose is 1mg/kg in the arterial line as a bolus at the start of dialysis. For patients with high haemorrhagic risk the recommended dose of enoxaparin is 0.5mg/kg in those with double vascular access or 0.75mg/kg for single vascular access.

Nadroparin:

Body weight (kg)	Volume to be injected into the arterial line at the start of each session. An additional dose may be given if dialysis lasts longer than 4 hours. (mL)
<50	0.3
50-69	0.4
>70	0.6

4.1.4 Treatment of unstable angina and non-Q-wave myocardial infarction

Dalteparin: 120 units/kg sc twice daily. Maximum dose 10,000 units/12hours. Continue treatment for 6 days.

Enoxaparin: 1mg/kg every 12 hours sc for a minimum of two and maximum of 8 days.

4.2 Dosing in the elderly

Elderly patients (arbitrarily defined as over 65) are regarded as being at risk for the development of venous thromboembolic events, so adequate prophylactic anticoagulant strategies are indicated. The mean age of the patients enrolled in the studies of Koopman[38] and Levine[31] was 60 years, with a standard deviation of 15 years. A significant proportion of patients was over 70 years of age in these studies, and doses were not altered. There may be no need to use a lower dose in generally fit elderly patients.

Guidelines in the product information for dosing in the elderly vary from "no adjustment necessary"[8,12,14] to "use with caution".[9] No specific dosing guidelines are available in this patient group.[109] However, doses may need to be decreased to take into account a higher risk of bleeding in elderly patients with: interacting medication, renal dysfunction and weight less than 50kg.

4.3 Dosing in Renal Failure

Since LMWHs are excreted by the renal route, doses may need to be reduced in

patients with a creatinine clearance of less than 60mL/min. The extent to which renal disease affects dosage is not clear.

The Concord Hospital protocol (N.S.W. February 1999) is as follows: Use recommended dose of LMWH if creatinine clearance >60mL/min. Reduce the initial dose by 25% if the calculated clearance is 30-60mL/min. Anti-Xa levels should be checked 3 to 5 hours after the morning dose on day 2 and every 2 days thereafter. If creatinine clearance <30mL/min, use UH.
Danaparoid: Reduce second and subsequent doses.[12]
Desirudin: Mean half-life in patients with end-stage renal failure is 52 hours. Monitor aPTT. If aPTT is over 85 seconds or twice the upper limit, stop infusion and reduce the dose accordingly.[14]

Note that the use of UH in patients with renal failure (creatinine clearance less than 30mL/min) and haemostatic defects is preferable, due to its shorter half-life and the ability of protamine to reverse its action.

5. FINANCIAL CONSIDERATIONS

When considering pharmacoeconomic aspects of therapy, both acquisition costs and clinical outcomes should be considered. Results are dependent on conditions and assumptions chosen. Direct costs include: drug costs, laboratory monitoring, phlebotomy charges, nursing time, costs of treating complications of therapy and bed charges. Indirect costs include quality of life issues such as discomfort, inconvenience and loss of wages. Models used to determine cost-effectiveness vary amongst investigators and depend on the type of institution, the country, whether costs are based on results reported in the literature or in one specific institution. Ideally, institution-specific economic evaluations are the most useful, especially if institution-specific factors such as rates of DVT, PE and standard therapy regimens are used. There have been several economic analyses of LMWHs and heparinoids in thromboprophylaxis of hip surgery.[19,110,111,112] Each of them has concluded that LMWH offers cost advantages when used routinely for thromboprophylaxis.

Hull[113] compared costs of tinzaparin sc daily vs warfarin for prophylaxis after orthopaedic surgery in 1436 patients in a double blind multicentre trial. His group found that the cost savings of $CAN2401 per patient using tinzaparin was not carried over in the US, because of differences in drug costs between the US and Canadian hospitals. A Swiss study[114] concluded that treatment of DVT with nadroparin in hospital was more cost-effective than treatment with either sc or iv UH. Savings of $US153 per patient were calculated, mainly due to decrease in administration and monitoring costs. Treatment efficacy and safety of nadroparin and UH were assumed to be the same and sensitivity analyses were carried out on the results to examine how robust primary assumptions in treatment duration and doses were. It should be noted that this trial was funded by the manufacturers of nadroparin.

Mol and Egberts[115] examined the costs of thromboprophylaxis in hip surgery in the Netherlands with no therapy, UH, LMWH, oral anticoagulants, dextran and danaparoid. Costs taken into account were diagnosis and treatment of DVT/PE, including venography, hospitalization costs and treatment monitoring. Although drug acquisition costs for danaparoid were the highest (140Netherlands Guilders, NLG) vs

heparin sc bd (22.4NLG) vs LMWH (24NLG), danaparoid was the most cost-effective modality overall. The main reason given for this result was the increased efficacy of danaparoid in the prevention of DVT. In this study, heparin, dextran and oral anticoagulant efficacy was based on studies from placebo-controlled studies, whereas the newer agents were assessed versus active controls. It should be noted, that this study was carried out in 1991 and supported by the manufacturer of danaparoid.

A Californian hospital pharmacy-managed program[116] successfully treated 55 patients with acute proximal DVT at home using enoxaparin and warfarin. There were no complications or hospital admissions for bleeding. The cost avoided by home treatment was estimated at $US547 per patient. It should also be noted that in Australia, if patients are discharged for home treatment, costs could be borne, in part, by the PBS.

Another economic evaluation assessed the cost effectiveness of LMWH compared to UH in both prophylaxis and treatment of DVT using data from published studies.[111] The results suggested LMWHs were more cost effective than UH for the *prophylaxis* of DVT in both general and orthopaedic surgery. LMWHs were also found to be more cost effective than both sc and iv UH in the *treatment* of DVT. Analysis did not include the morbidity or quality of life effects or side effects of therapy such as major bleeding complications or recurrent DVT/PE. All estimated costs from overseas studies were translated into NZ dollars. Nevertheless, the paper is a useful review of available literature on economic aspects of therapy.

Ting et al.[50] discussed an Australian hospital-in-the-home program for patients diagnosed in hospital with proximal DVT. Patients presenting to the Emergency Department and diagnosed with DVT were either admitted for 24 hours (53 patients with proximal DVT) or discharged after initial assessment (47 patients with distal DVT). Dalteparin sc was given daily for a minimum of 5 days by a nurse, who also monitored the patient's warfarin therapy, in the patient's home. There were no major bleeds, but two patients were withdrawn from dalteparin therapy because of minor bleeding. An estimated overall cost saving of $1239 per patient was realised, mainly in ward nursing costs. The advantages of early discharge should be tempered with correct patient selection as to diagnoses, extent of disease, supervision of at-home treatment and patient education about their therapy.[117]

Despite calls to "abandon the heparin pump",[118,119] there are a number of indications where UH continues to remain the treatment of choice. These include patients with a high risk of bleeding, acute renal failure, and extremes of weight, age or body shape.

In Australia, LMWHs are about ten times as expensive as UH in terms of acquisition cost, so it is important for each institution to define prescribing criteria based on clinical evidence. However, overall treatment costs are minimised in shorter inpatient stays, decreased monitoring costs and possibly increased effectiveness with decreased complications.

Clinical differences between LMWHs have not yet been shown in head-on comparison trials. The results of more studies will add to the information on hand, in order to assess the comparative efficacy of LMWH over UH in cardiac and in some

medical and general surgical patients. The potential cost savings for Australian hospitals with regard to monitoring costs and use of outpatient treatment should be evaluated.

ACKNOWLEDGEMENTS

We wish to acknowledge the assistance of all those who reviewed this document:
Members of NSW TAG, Dr Mark Herzberg, Westmead Hospital, Dr Kevin Rickard, RPAH, Dr Phillip Mondy, John Hunter Hospital, Dr Judith Trotman, St Vincents Hospital, Mr Barry West, Pharmacia&Upjohn Limited.

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